بسم الله الرحمن الرحيم

What is Cholestasis?

- **Cholestasis** is a general condition, common among many diseases associated with the **liver.**
- It happens when something goes wrong in **bile production** (a digestive fluid produced by the liver).
- Normally when a person ingests fats, the body uses bile as a catalyst in fat digestion and absorption.
- **Cholestasis** is caused by a disruption in the **synthesis of bile** in the liver that produces unwanted compounds in the blood circulation.

Cholestasis

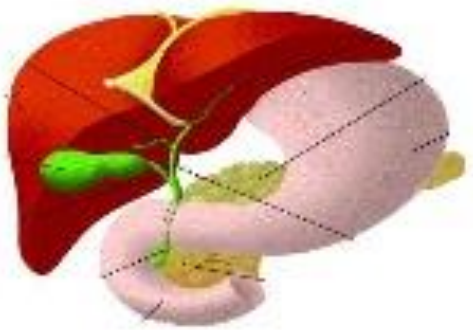
Definition –

Conjugated hyperbilirubinemia due to :

I. *Impaired bile formation (hepatocytes)*

II. *Impaired bile flow (bile ducts/ductules)*

Consequences of cholestasis



- **Secondary liver damage**
  - I. *Bile acid-induced hepatocyte injury*
  - II. *Secondary biliary cirrhosis*
- **Failure of substances secreted in bile to reach intestine**
  - I. *Bile acid deficiency in gut*
  - II. *Fat malabsorption/fat-soluble vitamin malabsorption*

Screening tests that suggest cholestasis –

Color change in skin/sclera/stool/urine

Biochemical tests (Alkaline Phosphatase , Bilirubin)

Enzymes raised in cholestasis

1) Alkaline Phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) & 5'-nucleotidase (5'NT).
2) ALP isoenzymes are also present in bone & placenta.
3) Increase in ALP, GGT & 5'NT → hepatobiliary origin.
4) GGT levels – Fatty liver, alcoholic liver disease.

Prothrombin time (PT) & (INR)

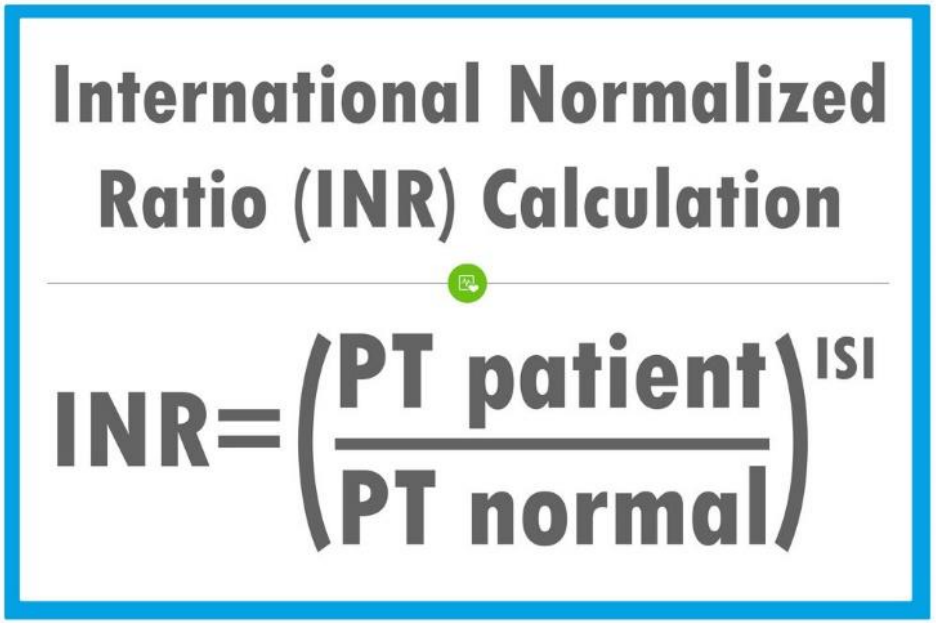
An increasing INR/PT - hepatocellular dysfunction.

(International normalized ratio)

May be deranged in cholestasis,

1. **But due to the malabsorption of Vit. K**
   - **Rapidly corrected by Parenteral administration of Vit K.**

The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system being used.



Diagnosis of jaundice

1- A bilirubin blood test will be done **(Total, Direct & Indirect).**
Other tests vary, but may include:

2- Hepatitis virus panel to look for infection of the liver
3- Liver function tests to determine how well the liver is working
4- Complete blood count to check for low blood count or anemia
5- Abdominal ultrasound
6- Abdominal CT scan **(Computed tomography)**
7- Endoscopic retrograde cholangiopancreatography (ERCP)
8- Percutaneous transhepatic cholangiogram (PTCA)
9- Liver biopsy
10 Cholesterol level
11 Prothrombin time

Table of diagnostic tests

Function test	Pre-hepatic Jaundice	Hepatic Jaundice	Post-hepatic Jaundice
Total bilirubin	Normal / Increased	Increased	increased
Conjugated bilirubin	Normal	Increased	Increased
Unconjugated bilirubin	Normal / Increased	Increased	Normal
Urobilinogen	Normal / Increased	Increased	Decreased / Negative
Urine Color	Normal	Dark (urobilinogen + conjugated bilirubin)	Dark (conjugated bilirubin)
Stool Color	Normal	Normal/Pale	Pale
Alkaline phosphatase levels	Normal	Increased	
Alanine transferase and Aspartate transferase levels		Increased	
Conjugated Bilirubin in Urine	Not Present	Present	
Splenomegaly	Present	Present	Absent

Intrahepatic Cholestasis of Pregnancy (ICP)

- ICP is a milder, subtype of cholestasis, the most common symptom of which is pruritus, or itch.
- Cholestasis of pregnancy is a condition where the flow of bile slows or stops.
- As a result, the bile enters the bloodstream and causes "intense or severe itching".

Intrahepatic Cholestasis of Pregnancy (ICP)

- ICP has been linked to premature delivery (الولادة المبكرة) and stillbirth (ولادة الجنين ميتا), therefore early delivery is often induced.

Intrahepatic Cholestasis of Pregnancy (ICP)

- Cholestasis of pregnancy usually occurs in the third trimester, a time when estrogen levels are increasing.
- Estrogen has been directly linked to disruption of bile production in the liver by acting on the channels that allow bile salts to be transported into and out of the liver.
- Estrogen has also been linked to cholestasis through indirect action such as altering the membranes of the cells that produce bile.

Pre Eclampsia (تسمم الحمل)

- **Pre-eclampsia (previously called toxemia) is a serious condition in which a pregnant woman develops high blood pressure.**
- **It ranges from mild to severe and may be fatal to both the mother and the baby. It affects liver with lower elevation in bilirubin and jaundice is uncommon.**
- **It usually develops after at least 20 weeks.**
- **The only way to stop it is to deliver the baby.**
- **Symptoms**

Headaches, Hypertension	Shortness of breath
Blurred vision, loss of vision	Abdominal pain
Nausea and/or vomiting	Kidney damage
Anemia	Thrombocytopenia

Acute fatty liver of pregnancy

- A serious complication unique to pregnancyb characterized by microvesicular fatty infiltration of hepatocytes **(Severe Pre Eclampsia).**
- It's a rare condition (1 in 7000-20,000 deliveries).
- It is more common with multiple gestations and possibly in women who are underweight.
- Acute fatty liver occurs typically in *the third trimester*.
- The foremost cause of AFLP is thought to be due to a mitochondrial dysfunction in the oxidation of fatty acids leading to an accumulation in hepatocytes
- The infiltration of fatty acids causes acute liver insufficiency**, jaundice is common.**

❖Jaundice Treatment

Treatment depends on the cause of the underlying condition leading to jaundice and any potential complications related to it. Once a diagnosis is made, treatment can then be directed to address that particular condition, and it may or may not require hospitalization.

1. Treatment may consist of expectant management (watchful waiting) at home with rest.

2. Medical treatment with intravenous fluids, medications, antibiotics, or blood transfusions may be required.

3. If a drug/toxin is the cause, these must be discontinued.

4. In certain cases of newborn jaundice, exposing the baby to special colored lights (phototherapy) or exchange blood transfusions may be required to decrease elevated bilirubin levels.

5. Surgical treatment may be required in case of obstruction jaundice.

Metabolic functions:- protein and ammonia metabolism

- Ammonia derived from amino acid and nucleic acid metabolism.
- Metabolised only in the liver:
- Urea cycle or Krebs Henseleit cycle
- Ammonia ⟶ Urea .
- Liver damage >80%- ↑ NH_3 & arginine conc. ⟶ Hepatic encephalopathy
- Degree of hepatic encephalopathy is proportional to NH_3 conc. in arterial blood .

Drug Metabolism

- Xenobiotics are metabolised – microsomes of liver CYP 450
- Detoxification – 2 phases
  phase 1-oxidation/hydroxlation
  phase 2-conjugation with polar compound
- Severe liver injury - ↓ability to metabolise drugs- measure extent of liver damage in known liver disease

Synthetic functions:- protein synthesis

- Liver – site for synthesis for most plasma proteins(100% albumin) exceptions- immunoglobulins
- Extensive liver destruction-↓serum total proteins and albumin
- Cirrhosis - + ↓ delivery of amino acids
- Common causes of ↓ S.proteins : renal diseases, liver disease, malnutrition, protein losing enteropathy, chronic inflammatory diseases
- ↓S.proteins levels –depend on t½ of protein
  eg: albumin- 20 days , transthyretin – 1-2 days
  factor VII- 4-6hrs , transferrin – 6 days

Prothrombin time (PT)

- Most frequently used – liver associated coagulation abnormalities- best index of severity
- Efficacy of extrinsic clotting system- factor VII
- Factor VII- synthesized in liver- evaluate liver function
- PT part of MELD score- Model for End stage Liver Disease

  -evaluating priority- Liver Transplantation - predicts 3 month mortality for cirrhotic **patients**

MELD Score: Bilirubin, Creatinine, PT, INR (International Normalized Ratio)

Problems with using PT

- Non-specific – elevated in most coagulation disorders
- In cholestasis – with normal hepatocyte **function**

↑ PT - ↓ bile salts - ↓ absorption of vit K

- ↓ factors II, VII, IX, X

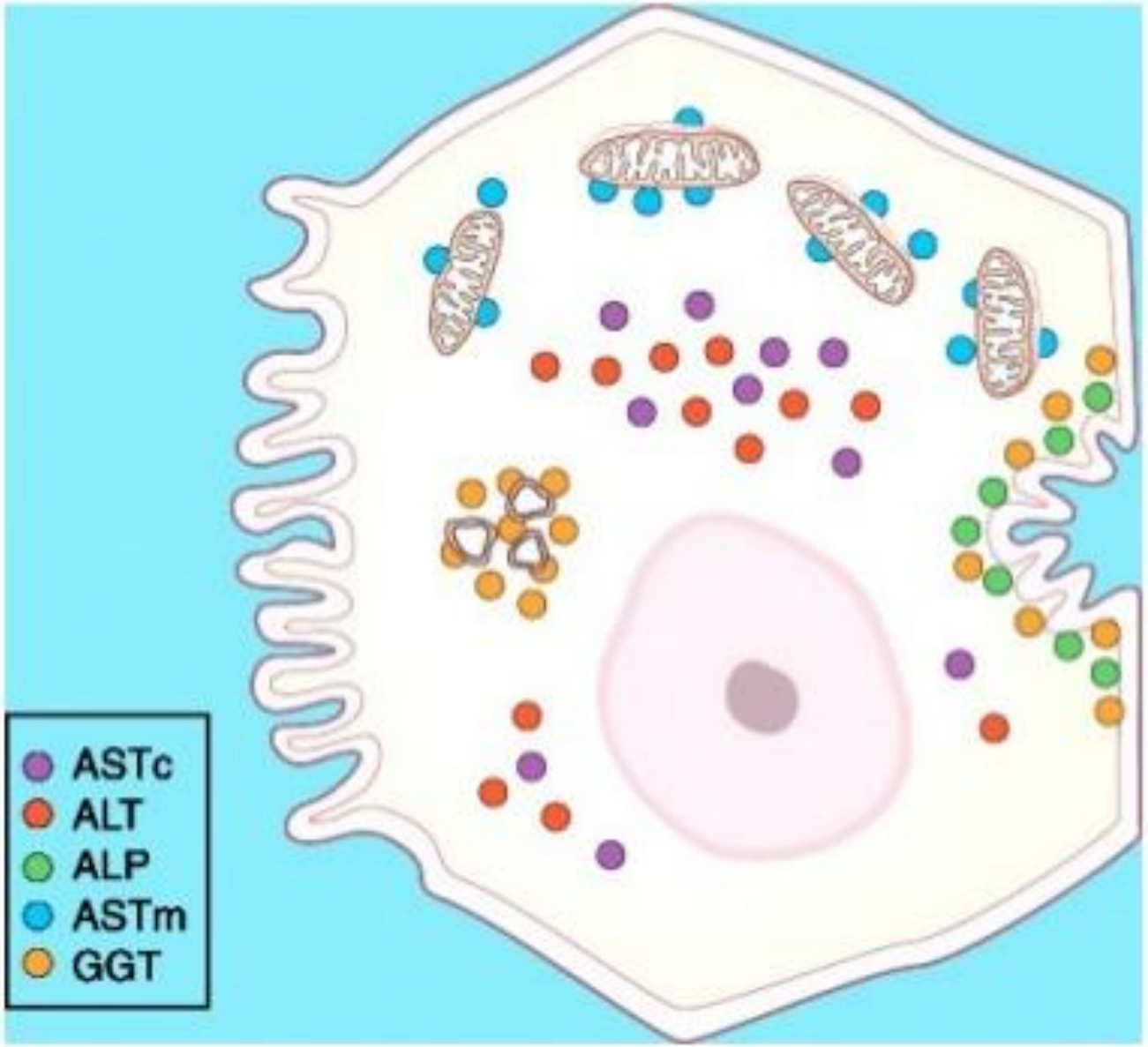
cholestasis- precursor forms of clotting factors increased

Tests of Liver Injury

Plasma Enzyme Levels

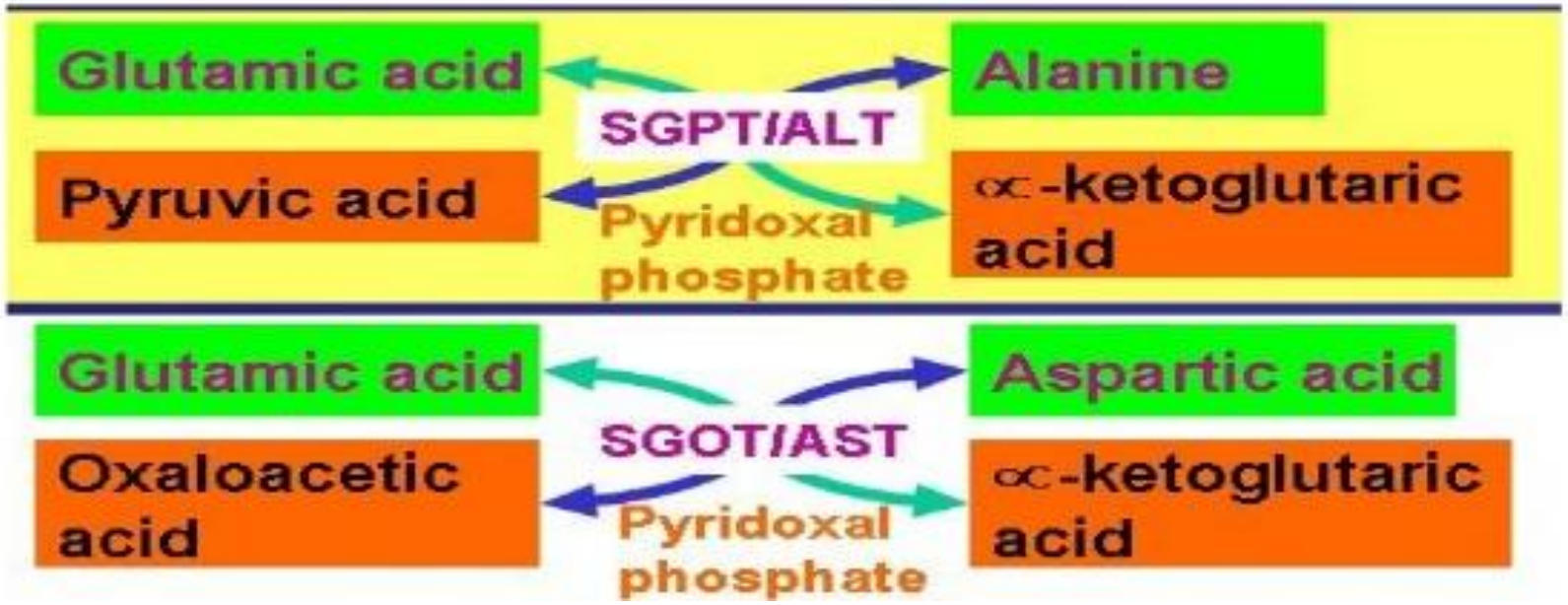
1- Aspartate Aminotransferase (AST)
2- Alanine Aminotransferase (ALT)
3- Lactate Dehydrogenase (LDH)
4- Alkaline Phosphatase (ALP)
5- Gamma Glutamyl Transferase (GGT)
6- 5‘- Nucleotidase

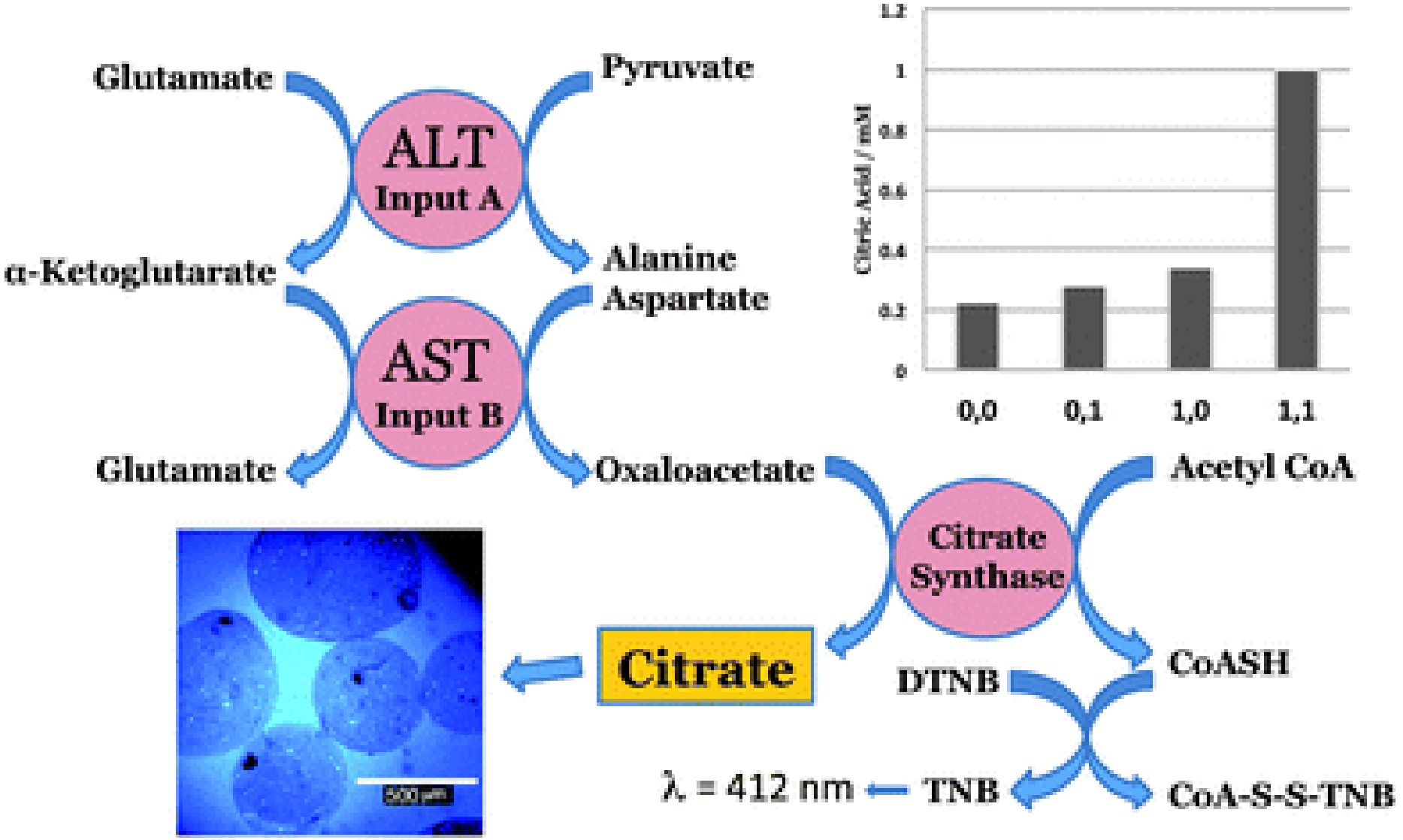
Cellular location of enzymess



Aminotransferases (Transaminases)

- Aspartate Aminotransferase(AST) =Serum Glutamate Oxaloacetate Transaminase (SGOT)
- Alanine Aminotransferase(ALT) = Serum Glutamate Pyruvate Transaminase(SGPT)




Glutamate
Pyruvate
ALT
Input A
α-Ketoglutarate
Alanine
Aspartate
AST
Input B
Glutamate
Oxaloacetate
Acetyl CoA
Citrate Synthase
Citrate
CoASH
DTNB
λ = 412 nm
TNB
CoA-S-S-TNB
Citric Acid / mM
1,2
1
0,8
0,6
0,4
0,2
0
0,0
0,1
1,0
1,1

AST- liver, heart skeletal muscle, kidneys, brain, RBCs

- In liver 20% activity is cytosolic and 80% mitochondrial
- Clearance performed by sinusoidal cells,
- AST cytosolic t½ -17hrs
- AST mitochondrial t½ - 87hrs
- Used for monitoring therapy with hepatotoxic drugs if levels >3 X normal stop therapy

ALT – more specific to liver, very low concentrations in kidney and skeletal muscles.

- In liver totally cytosolic.
- t½ - 47hrs
- Used in non alcoholic, asymptomatic p **patients**

Aspartate aminotransferase (AST)

organ	AST	ALT	organ	AST	ALT
heart	156000	7100	pancrease	28000	2000
liver	142000	44000	spleen	14000	1200
skeletal	99000	4800	lung	10000	700
kidney	91000	19000	serum	20	16

- **Both these enzyme are found in most tissues , but the relative amounts vary . heart muscles are richer in AST, whereas liver contains both but more of ALT.**

Levels of AST & ALT

- AST is assessed along ALT in monitoring liver damage.
- These two values normally exist in an approximately 1:1 ratio. **Or AST/ALT Ratio = 0.8**
- As a rough guide:
  - AST>ALT in:
    1- alcoholic hepatitis and cirrhosis,
    2- metastatic cancer of the liver
    3- and non-biliary cirrhosis,
  - while ALT>AST in:
    1- • viral and drug hepatitis,
    2- • chronic hepatitis C
    3- Extra – hepatic obstruction.

Clinical significance of AST: ALT ratio

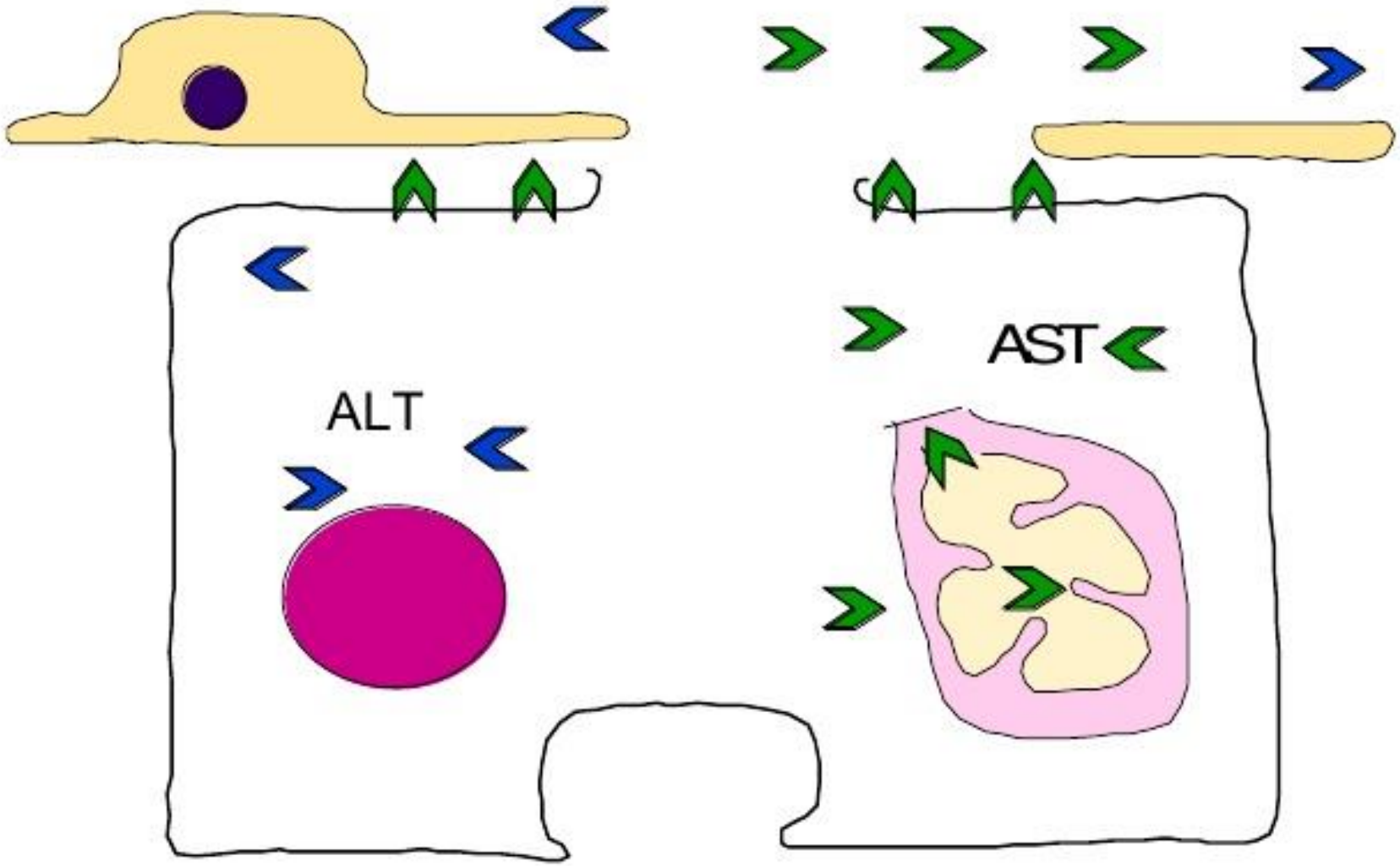
Normal AST: ALT ratio is 0.8. A ratio >2 is seen in

1- Alcoholic hepatitis
2- Hepatitis with cirrhosis
3- Nonalcoholic steatohepatitis (NASH)
4- Liver metastases
5- Myocardial infarction
6- Erythromycin treatment

A low ratio (ALT is higher) is seen in

1- Acute hepatocellular injury
2- Viral hepatitis.
3- Extrahepatic obstruction (cholestasis)

Release of AST/ALT from Liver Cells After Alcohol Exposure



Alcohol increases mitochondrial AST on liver cell plasma membrane where it readily enters blood. Thus AST>>ALT in blood.

Aminotransferases (cont..)

- ***Acute hepatocellular injury*** -
  > 24hrs - AST < ALT

- ***Alcoholic hepatitis*** (alcohol induced hepatocyte injury)- AST >ALT
  - mitochondrial damage induced – ASTm released – has a longer t½ & is the predominant AST in hepatocyte
  - ↑↑ AST:ALT → 3-4 : 1 – **DeRitis Ratio**
  - ↑ **ASTm** is s/o advanced alcoholic liver disease

- ***Chronic liver injury*** (mainly cirrhosis) – ALT > AST
  -but as fibrosis progresses – ALT↓ & ↑ AST:ALT

- ***End stage liver cirrhosis*** – AST and ALT levels NOT elevated
  - massive tissue destruction

- ***Acute fulminant hepatic failure*** - ↑↑AST and ↑↑ ALT ,
  AST:ALT > 1

AST:ALT ratio

- Alcoholic hepatitis
  - Ratio is >1 90% of the time – often 2:1
  - Mechanism thought to be related to B6 depletion in alcoholics which leads to disrupted ALT synthesis and therefore decreased levels.
  - This is NOT SPECIFIC!!
- Viral Hepatitis: *Both ALT AND AST elevated*
- Ratio < 1 70% of the time
  - Mechanism unclear

Liver Function Tests

- In hepatocellular disease (e.g. hepatitis) plasma levels of transaminases reach of 10 – 100 fold the upper reference limit.
- In uncomplicated cholestasis (obstruction) ALT and AST levels may be increased, but usually to less than 10 times the upper reference limit.

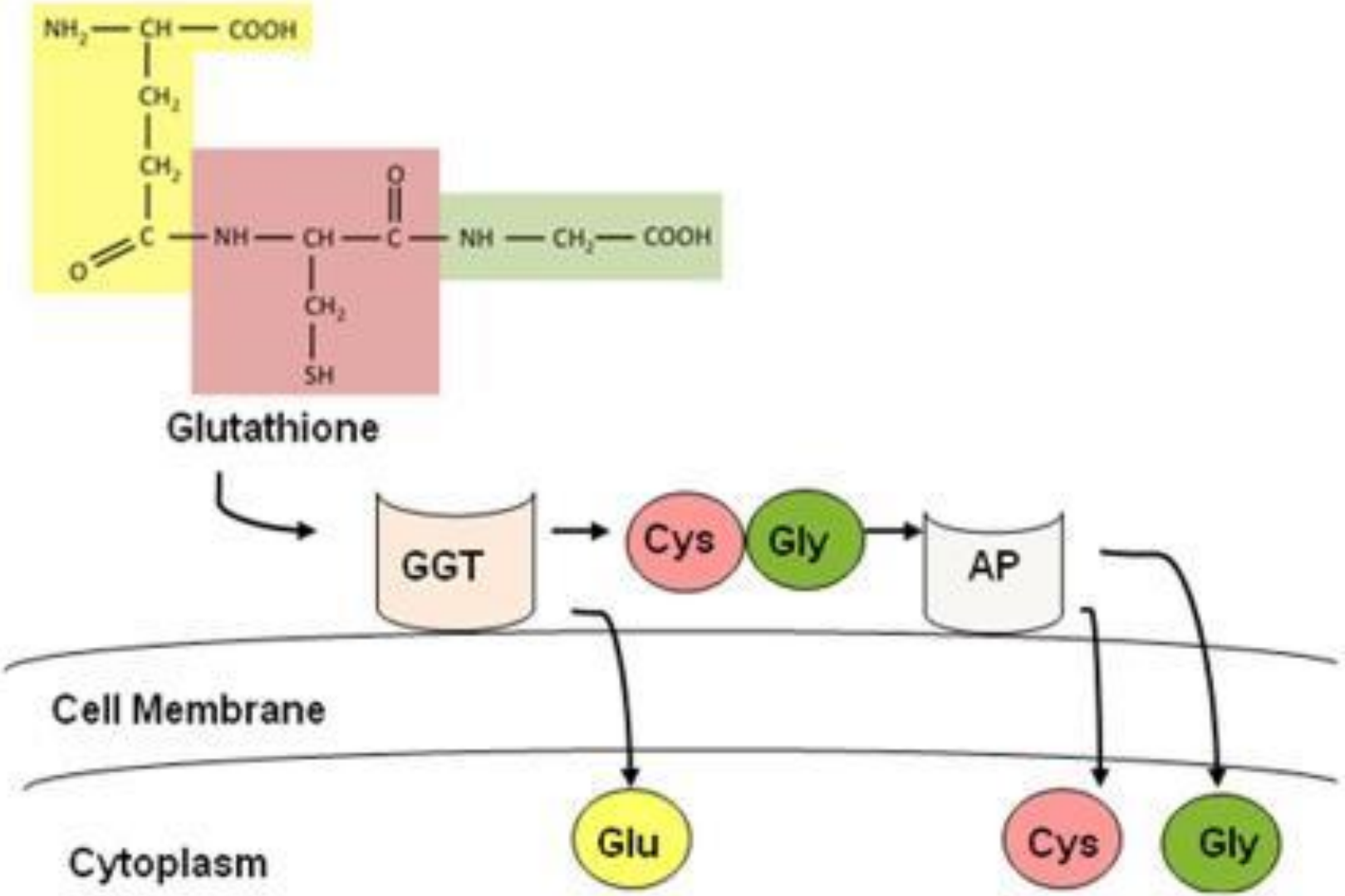
Enzymes – canalicular injury
Markers of Cholestasis

Alkaline Phosphatase (ALP) –

- liver and bone (placenta, kidneys, intestines)
- Hepatic ALP present on surface of bile duct epithelia- canalicular surface and accumulating bile salts increase its release from cell surface – in biliary dysfunction (not cell injury).
- Takes time for induction of enzyme levels so may not be first enzyme to rise and half-life is 3 days
- ALP isoenzymes, 5-NT or gamma GT may be necessary to evaluate the origin of ALP
- Normal = 30-120 IU/L
- Causes of ↑ in ALP: biliary tract obstruction –eg: Stones
  hepatitis
  ascending cholangitis

Gamma Glutamyl transferase (GGT)

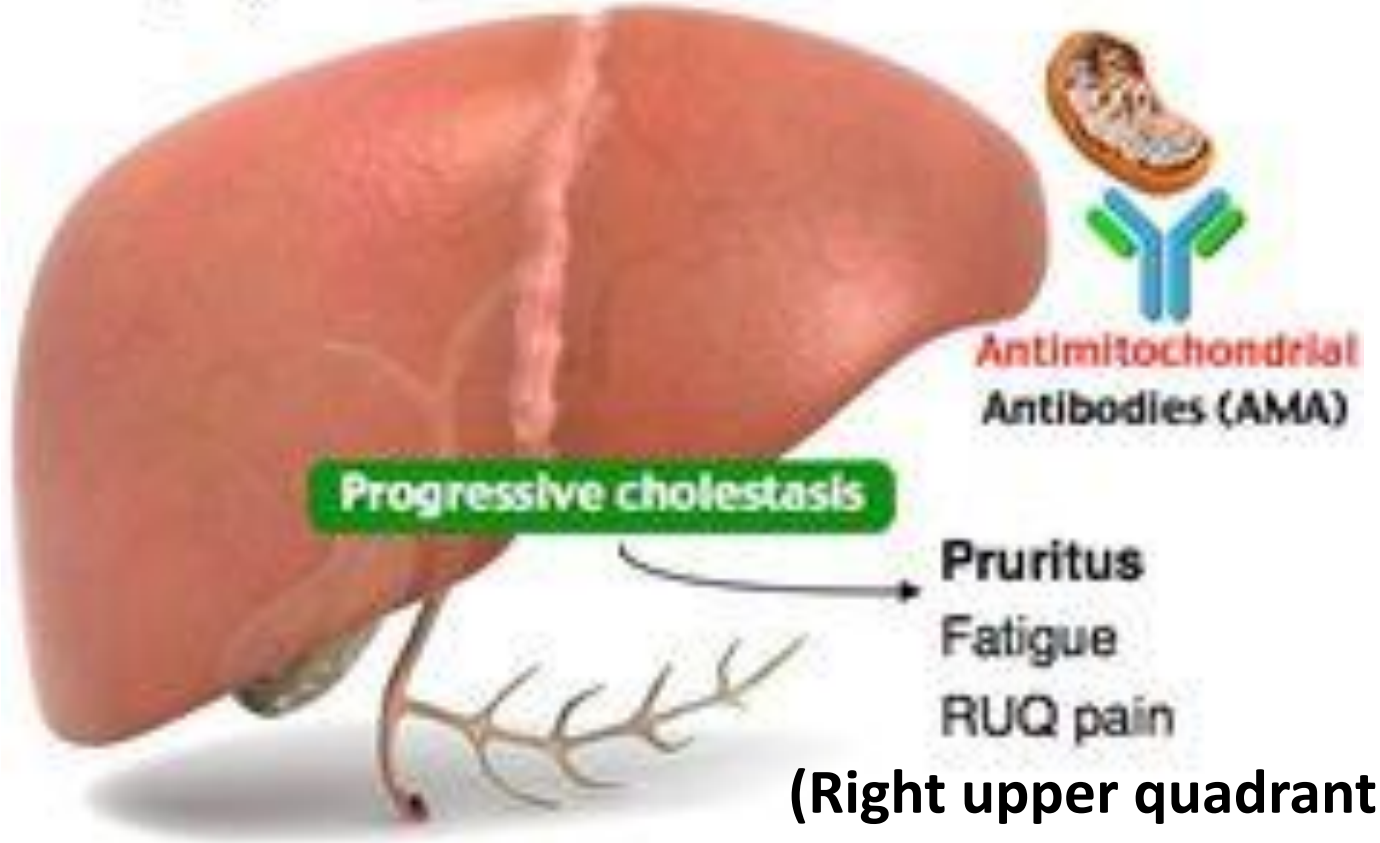
- Regulates transport of AA across cell membrane
- hepatocytes and biliary epithelial cells, pancreas, renal tubules and intestine
- Confirm hepatic source for a raised ALP
- Half life -10 days
- Very sensitive but Non-specific
- Raised in ANY liver disease hepatocellular or cholestatic
- Highest values – 10 x –chronic cholestasis: PBC,
- Chronic alcohol abuse – 60-70% show ↑ GGT
  -correlation between amount of alcohol intake & GGT activity -remains elevated 1 month after alcohol abstinence
  -t½ ↑ to 28 days
- Cholestasis of pregnancy : ↑ ALP, but GGT remains normal



Hydrolysis of extracellular glutathione by GGT1. GGT1 releases glutamate and cysteinyl-glycine. Cysteinyl -glycine is hydrolyzed by aminopeptidases (AP) releasing cysteine and glycine. All three amino acids can then be taken up into the cell. Glutathione can not be taken up intact by most cells.

Primary Biliary Cirrhosis (PBC)

Slow progressive destruction of the small bile ducts



(Right upper quadrant)

↑ Gamma-glutamyltransferase (GGT)
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)

6-Gamma glutamyl transferase (GGT)

- Gamma glutamyl transferase (GGT), or gamma glutamyl transpeptidase, may be measured in the blood to check the difference between bone ALP and liver ALP.
- High levels of GGT are present when the liver is damaged but not present with bone disease. A high level of GGT may be caused by alcohol use or may mean that blocked bile ducts are causing inflammation.
- The level of GGT may be high with the use of certain medicines, such as phenytoin and phenobarbital.
- In some medical centers, a test that measures **5-nucleotidase** is done instead of the GGT test because it is better at finding liver disease.

The enzyme:

1-

- GGT is ↑ in:-alcoholics without liver diseas

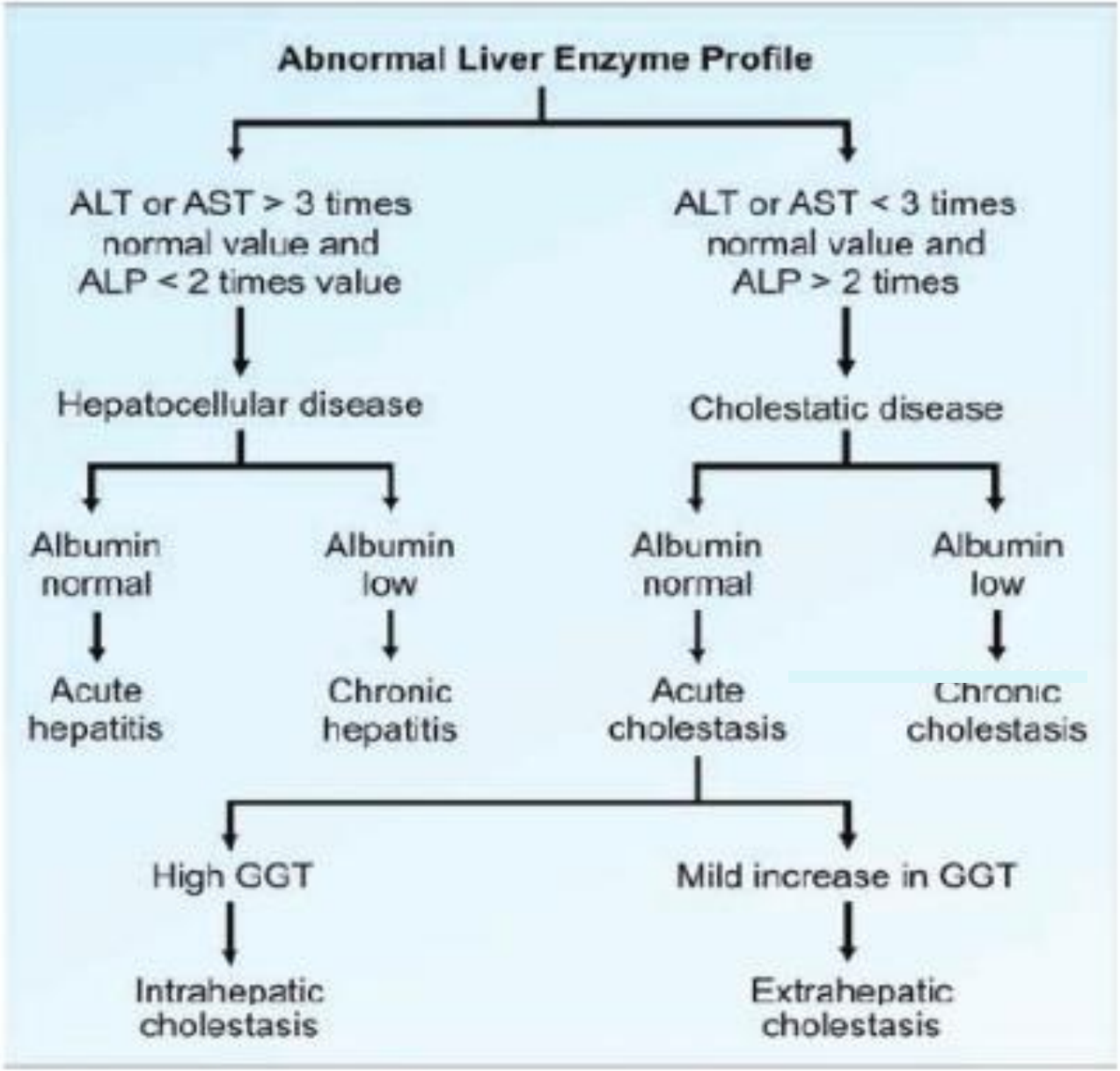
2– obese **patients**

3– high conc.of drugs: acetaminophen, phenytoin, carbamazepine(GGT ↑ to restore glutathione used to metabolise drugs)

- Isolated increase does not require any further evaluation, suggest watch and repeated quarterly,or if other LFT's become abnormal then investigate
- GGT Assay: substrate - ɣ glutamyl-p nitroanilide → **p nitroaniline** liberated (chromogenic) – measured spectrophotometrically

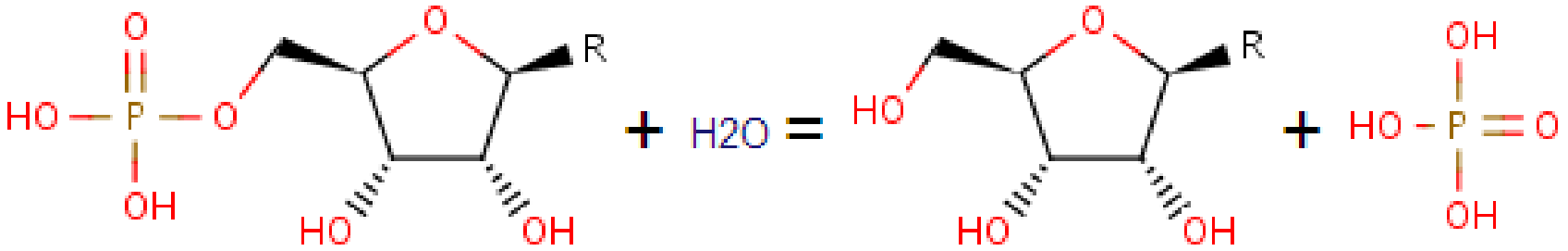
Algorithm for Diagnosis of Liver Disease

Algorithm for Diagnosis of Liver Diseases



5’-Nucleotidase

Reaction catalyzed by 5'-nucleotidase (3.1.3.5)



a 5'-ribonucleotide + H2O = a ribonucleoside + phosphate

- Despite its widespread distribution in the human body, serum elevations of 5NT are medically useful in identifying hepatobiliary disease.

The test can be used in conjunction with elevated alkaline phosphatase levels or other clinical findings suggestive of liver/gall bladder disease.

- GGT can be used in a similar manner, but, generally, GGT levels are elevated in any hepatocellular injury, while 5NT is more specific to situations resulting in obstructive or cholestatic liver disease.

5’-Nucleotidase (5NT) levels are elevated during the following:

- Obstructive or cholestatic liver disease
- Hepatitis
- Intrinsic liver damage
- Primary liver malignancy and metastasis
- Biliary cirrhosis
- Use of hepatotoxic drugs

Lactate dehydrogenase (LDH)

- Cytosolic glycolytic enzyme
- Lactate $\xrightarrow{\text{oxidation}}$ Pyruvate
- 5 major isomers : LD_1 – LD_5
- **LD1** & LD2 – cardiac muscle,kidney,RBCs
- **LD4** & LD5 – liver , skeletal muscle
- t½ - 4-6hrs , 500X plasma conc.
- Normal levels upto 150 IU/dl
- ↑↑ hepatitis- transient-normal –clinical presentation
- ↑↑ total LDH > 500 IU/dl

  ↑↑ ALP > 250 IU/dl

  in absense of abnormality in AST or ALT

  Indicate SOL – s/o metastatic Ca, HCC, hemangioma


Thank You
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